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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/983,020	10/22/2001	Steven W. Homans	1496-205	7728

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EXAMINER

BORIN, MICHAEL L

ART UNIT PAPER NUMBER

1631

DATE MAILED: 06/08/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/983,020	Applicant(s) HOMANS ET AL.	
	Examiner Michael Borin	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 05 April 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) 15 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Status of Claims

1. Response filed 04/05/2004 is acknowledged.

Claims 1-15 are pending. Claim 15 remain withdrawn from consideration.

Applicant's arguments have been fully considered but were not deemed persuasive for the reasons stated below. The following rejections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 102 and 103.

The following is a quotation of the appropriate paragraphs of 35 U.S.C.102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103[©] and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1,2,4-13 are rejected under 35 U.S.C. 102(a) as anticipated by Al-Hashimi et al (J. Magnetic Resonance, 2000, Vol. 143, 402-406).

The claims are drawn to method for determining the global fold of a peptidic molecule which comprises the steps of: subjecting a molecule having ¹³C and/or ¹⁵N substitutions on the backbone to NMR analysis in a non-aligned medium; placing said molecule in a first and second states of partial alignment and measuring residual dipolar couplings in said first and second states of partial alignment, wherein the magnitudes and orientations of the principle axes of the alignment tensors are known or obtained; varying computationally by increments the .phi., .psi. angles for a first amino acid of said molecule; minimizing the rigid-body orientation of said first amino acid and a second amino acid adjacent in the peptidic sequence to said first amino acid with respect to both tensor frames simultaneously; calculating the minimum difference between measured and calculated dipolar couplings for each of said first and second

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amino acids; deriving the ϕ , ψ angles and orientation of the dipeptide fragment composed of said first and second amino acids; and repeating the above steps for each sequential dipeptide fragment of said molecule to obtain a global fold of the peptidic molecule.

Al-Hashimi et al teach method for determining complete three-dimensional structure (i.e., global fold) of a protein by based on tensor analysis and combining residual dipolar couplings from two different alignment media. The measurements are based on ^{15}N - ^1H dipolar coupling signals; the latter may be further supplemented by ^{13}C - ^1H dipolar coupling data. The method is based on rotating and aligning successive, fragment-centered order tensor frames. Possible orientations obtained from two alignment media are determined, compared and the alignment having minimal difference is identified as corresponding to correct fold. Up to five order tensor parameters are measured for each medium. Further, the reference teaches that in real situation the method can be applicable to molecular fragments in proteins for which local geometry can be inferred from their backbone NOE without the necessity to collect side chain data.

It is the Examiners position that all the elements of Applicant's invention with respect to the specified claims are instantly disclosed by the teaching of the reference cited above.

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3. Claims 1-14 are rejected under 35 U.S.C. 103(a) as obvious over Mueller, G. et al (Journal of Molecular Biology 2000, Vol. 300(1), pages 197-212) in view of Al-Hashimi et al. The rejection is maintained for the reasons of record.

Mueller, G. et al. teach method for determining the global fold of maltodextrin-binding protein by refining of NMR analysis of the protein obtained from measurements in non-aligned medium with dipolar coupling restraints obtained from measurements of dipolar couplings in partially aligned state in liquid crystal medium.

The reference does not teach measurement of dipolar couplings in two different steps of partial alignment. However, Al-Hashimi et al, discussed in the rejection above, teach that the method can be improved by measuring dipolar couplings in more than one medium because determining of relative fragment orientations based on a single set of residual dipolar couplings is inherently hindered by the multi-valued nature of the angular dependence of the dipolar interaction. Even with unlimited dipolar data, this gives rise to a fourfold degeneracy in fragment orientations. Measuring in two different media completely removes this degeneracy by combining residual dipolar coupling measurements from two alignment media. Thus, it would have been prima facie obvious at the time the invention was made to be motivated to improve method

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of Mueller by measuring partial alignment in two different states as described by Al-Hashimi.

Response to arguments

Applicant argues that the Mueller et al reference includes steps other than those claimed for the instant methods. However, the instant claims have open-ended "comprising" language and thus can include steps other than claimed. Further, the protocol for choosing possible orientations established based on dipolar coupling data illustrated on Figure 4 does not seem to be based on large number of NOEs; rather, the results are being compared with data derived on the basis of NOE (what corresponds to instant claim 9). Further, Examiner disagrees that the Mueller et al reference does not teach labeling of backbone but requires labeling side chains; the referenced method includes labeling of both backbone and side chains.

In regard to Al-Hashimi reference, applicants argue that the reference does not achieve the global fold of the studied fragments. First, Fig. 3 displays reassembled zinc rubredoxin protein. Second, the referenced method is addressed as a "direct approach for unambiguously determining relative orientation of known molecular fragments" and is intended for "rapidly determining protein backbone structures for unknown proteins"(see Discussion, first and last paragraphs). Further, applicant assert that Al-

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Hashimi's method should be supplemented by 1H - 1H or ^{13}C - 1H data. Contrary, however, the method is based solely on ^{15}N - 1H data; the reference indeed mentions ^{13}C - 1H data as optional information that might be useful as a descriptor of secondary structure of protein fragments (see Discussion, last paragraph).

As for motivation to combine the references The rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art. The strongest rationale for combining references is a recognition that some advantage or expected beneficial result would have been produced by their combination. In the instant case such motivation comes from the notion that measuring in two different media (as in Al-Hashimi) completely removes degeneracy in protein orientations obtained in a single alignment medium (as in Mueller) and allows unambiguous determining of protein structure.

Double Patenting

4. Claims 1-14 of this application conflict with claims 1,3-15 of Application No. 10/164716. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one

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application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Borin whose telephone number is (571) 272-0713. Dr. Borin can normally be reached between the hours of 8:30 A.M. to 5:00 P.M. EST Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0549.

June 4, 2004

MICHAEL BORIN, PH.D
PRIMARY EXAMINER

mlb

